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CLINICAL STUDY

Gastric Emptying in Patients on Renal Replacement Therapy

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ABSTRACT

In addition to gastrointestinal tract symptoms such as nausea, vomiting, and loss of appetite, impaired gastric emptying time (GET) may be related to nutritional parameters and nutritional status of patients on renal replacement therapy (RRT). Patients on RRT are affected by several factors such as uremic toxins, the presence of dialysate in the peritoneal cavity, and the drugs used against renal allograft rejection. In this study, we investigated the gastric emptying time and its relationship with biochemical and nutritional parameters in patients on RRT: those on hemodialysis and peritoneal dialysis, and renal transplantation patients. Seventy-five patients, 44 on hemodialysis, 16 on peritoneal dialysis, and 15 renal transplant patients, were included in the study. They were examined for gastric emptying time using a radioisotopic method. The results were compared with the GET of healthy subjects. Each group of patients was evaluated in terms of hemoglobin, hematocrit, blood urea nitrogen (BUN), creatinine, blood glucose, total protein, albumin, serum lipids, parathyroid hormone (PTH) and body mass index and biceps and triceps skinfold. The mean GET of patients on RRT was significantly longer than the mean GET of healthy subjects (87.8 ± 23.4 vs. 55 ± 18 min, $p < 0.05$). The mean GET of each therapy subgroups was significantly longer than the healthy subjects (the mean GET was 85.1 ± 22.4 min for hemodialysis, 87.7 ± 31.8 min for peritoneal dialysis, and 94.6 ± 16.7 min for renal transplant patients, respectively, $p < 0.05$). On the other hand, the differences in the mean GET between the three therapy subgroups were not statistically significant ($p > 0.05$). In addition, time on replacement therapy inversely and blood glucose positively correlated with GET in renal transplant patients. In conclusion, GET was

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longer in patients on all three RRT modalities than in healthy subjects. GET was not significantly different in dialysis patients and renal transplant patients.

Key Words: Gastric emptying; Hemodialysis; Peritoneal dialysis; Renal transplantation.

INTRODUCTION

Complications involving the gastrointestinal tract are common in patients with end-stage renal disease (ESRD). Nausea, vomiting, and loss of appetite are among the main symptoms in patients with ESRD.^[1] All these symptoms are related to malnutrition, which increases cardiovascular events, morbidity, and mortality in dialysis patients. Although urea, creatinine, or other uremic toxins can be removed by hemodialysis treatment, delayed gastric emptying time (GET) is reported by many authors.^[2–5] In addition to impaired gastric emptying time in ESRD, increased intraabdominal pressure and presence of glucose-containing dialysate cause an additional delay in gastric emptying time in peritoneal dialysis patients, despite the uremic toxins removal.^[6–8] Renal transplantation offers good renal function similar to native kidneys. Renal transplant patients with functional graft are expected to have normal GET. Nevertheless, immunosuppressive treatments used after transplantation may have side effects on gastric motility. On the other hand, gastroparesis is an important aspect when determining which drug should be prescribed.

The improvement in hemodialysis and peritoneal dialysis techniques and the more beneficial immunosuppressive agents are used to prevent and reverse the adverse effects of ESRD. However, there are still some points that need to be investigated and corrected for those patient group. In the literature, the effect of each replacement therapy was compared with healthy subjects or each other. However, there is scarce knowledge about determining the impact of all three RRT groups on GET. A feasible noninvasive scan technique, using food with technetium-99m labeled sulphur colloid radioisotopes, has been used to measure gastric emptying in patients with renal disease as well as in nonuremic subjects.^[6,9–11]

The aims of the study were to examine the GET in patients on RRT and compare it with the GET of healthy subjects, and to determine the relationship between GET and biochemical-nutritional parameters.

PATIENTS AND METHODS

The study included 75 patients on RRT; 44 hemodialysis patients, 16 peritoneal dialysis patients,

and 15 renal transplant patients. The study was conducted in accordance with the ethical standards of Gazi University. The patients were given information about the purpose of the study before they gave their voluntary consent. All patients were on replacement therapy for more than three months. The patients with known previous gastric surgery, those with a peptic ulcer disease, amyloidosis, systemic sclerosis, or other collagen vascular disease were excluded from the study. None of the patients had upper gastrointestinal obstruction in their previous endoscopic examinations. The patients diagnosed with diabetes mellitus or autosomal polycystic kidney diseases were also discharged from the study.

Hemodialysis Characteristics

Hemodialysis patients were dialyzed three times weekly for 4 hr with bicarbonate dialysate and hemophane membrane. Blood flows were adjusted according to patients' body weight, and dialysate flows were 500 mL/min. These patients underwent radioisotopic scanning on a midweek dialysis free day. At the time of study, all patients were in a clinically stable condition. All patients routinely received oral vitamin B complex and vitamin C daily, and folic acid after each hemodialysis session.

Peritoneal Dialysis Characteristics

Nine peritoneal dialysis patients were treated with continuous ambulatory peritoneal dialysis (CAPD) and seven patients with continuous cycler peritoneal dialysis (CCPD). Peritoneal dialysis fluid was lactate-based dialysate with glucose concentration ranging from 1.36–3.86 g/L. CAPD patients were using four exchanges per day of 2–2.5 L, and CCPD patients 10 L per night and 2 L per day. The GET was studied with their abdomen full of dialysate, to mirror similar conditions in their daily life. Vitamin B complex and vitamin C were administered orally daily to all patients. All the peritoneal dialysis patients were free from peritonitis for at least three months.

Renal Transplant Characteristics

The patients had stable renal graft function when the study was conducted and acute rejection free period

was at least three months. The immunosuppressive treatment of renal transplant patients were as follows: steroid, cyclosporine, and mycophenolate mofetil (MMF) in seven patients; steroid, cyclosporine, and azathioprine in four patients; steroid, tacrolimus, and mycophenolate mofetil (MMF) in three patients; and steroid, tacrolimus, and azathioprine in one patient. GET study was begun at 8:00 a.m. The patients were able to take their immunosuppressive therapy at 10:00 a.m., as the usual time.

Gastric Emptying Test

GET was measured by scintigraphic method using radioisotopes. The test was performed in the morning after an overnight fast. Medications, which can affect the gastric motility, were not prescribed. To avoid possible diurnal variations, all the studies began at 8.00 am. Patients consumed a meal consisting of two scrambled eggs on two pieces of bread with butter and 150 mL water in a sitting position in 10 min. The egg substituted was radiolabeled using 400 μ Ci of technetium-99m labeled sulphur colloid, which was mixed into liquid egg substitute preparation. The labeled mixture was then scrambled in a non-stick frying pan with a portion of butter. The total caloric value of the meal was 420 cal. Anterior images of the gastric region were taken in the supine position within 1 min of the completion of the meal. Dynamic images were acquired for 15 min at a rate of one frame per minute; subsequent images were obtained every 15 min until more than half of the meal had emptied from stomach. Images were obtained using a gamma camera (Starcam 4000 XRT General Electrics, US) with a 20% energy window centered on the 140-keV ^{99m}Tc photopeak on. Analysis of gastric emptying was performed as follows: for each image, the gastric region was drawn manually using a computer joystick. Time-activity curves generated from the gastric region of interest and the half-time ($T_{1/2}$) for gastric emptying time were determined. The gastric emptying times were compared with the results of the healthy subjects, which were obtained from the nuclear medicine department. The mean GET had been calculated as 55 ± 18 min for healthy, nonsymptomatic subjects in the nuclear medicine department.

Biochemical Analysis and Anthropometric Measurements

Hemoglobin (Hb), blood urea nitrogen (BUN), serum creatinine, blood glucose, total protein, albumin, total cholesterol (t-chol), HDL-cholesterol (HDL), LDL-cholesterol (LDL), VLDL-cholesterol (VLDL), triglyceride, sodium (Na^+), potassium (K^+), calcium

(Ca^{++}), phosphorus (P), intact parathyroid hormone (iPTH), ferritin, vitamin B_{12} (vit B_{12}), and folic acid were collected for each patient from patient files at the same time of the study and then three months later. The mean value of the two different tests were calculated and used for the statistics.

Body mass index (BMI) was determined with the formula body weight (kg)/length (m^2). Biceps and triceps skinfolds were measured three separate times with a conventional skinfold caliper by a single observer, and the mean values were recorded. The measurements were performed on the nonaccess arm of each patient after their dialysis session in hemodialysis patients, and routine control in peritoneal dialysis and renal transplant patients.

Statistics

Data were expressed as means $\pm$ standard deviation (SD), and analyzed with SPSS 10.0 for Windows. The analyses were performed by the one sample *t*-test, Mann-Whitney U, Kruskal-Wallis test, Pearson correlation when appropriate. Results are considered statistically significant for *p* less than 0.05.

RESULTS

The mean ages were 34.9 ± 9.5 years for all patients, 35.3 ± 12.4 years for hemodialysis patients, 41.8 ± 7.4 years for peritoneal dialysis patients, and 33.6 ± 7.9 years for transplant patients. The mean age of patients, the mean duration on therapy, and BMI were not statistically different between the three treatment groups ($p > 0.05$). The demographic features of patients are shown on Table 1.

The mean GET was 87.8 ± 23.4 min for all patients on RRT, and significantly longer than the mean GET of healthy subjects (55 ± 18 min) ($p < 0.05$). The mean GETs were 85.1 ± 22.4 min in hemodialysis patients, 87.7 ± 31.8 min in peritoneal dialysis patients, and 94.6 ± 16.7 in renal transplantation patients. The mean GETs of each therapy subgroups were significantly longer than the healthy subjects ($p < 0.05$). On the other hand, there was no significant difference between the therapy subgroups ($p > 0.05$). In addition, no differences between men and women were found when analyzing GET data in each therapy subgroup.

None of the following parameters demonstrated a significant correlation with the GET in hemodialysis and peritoneal dialysis patients ($p > 0.05$): patients' age, duration on RRT, the level of Hb, BUN, creatinine, blood glucose, total protein, albumin, t-chol, HDL,

Table 1. Demographic features of patients (mean $\pm$ SD).

Replacement therapy	Hemodialysis	PD	Renal transplantation
n	44	16	15
Male/female	29/15	10/6	10/5
Age (years)	35.3 $\pm$ 12.4	41.8 $\pm$ 7.4	33.6 $\pm$ 7.9
Time on therapy (months)	29.5 $\pm$ 29.4	22.5 $\pm$ 22.2	27.7 $\pm$ 18.0
Body mass index (kg/m ²)	24.1 $\pm$ 5.3	27.1 $\pm$ 4.4	24.3 $\pm$ 4.2

Abbreviation: PD=Peritoneal dialysis.

LDL, VLDL, triglyceride, Na⁺, K⁺, Ca⁺⁺, P, iPTH, ferritin, vitB₁₂, or folic acid. However, in all of those parameters, an inverse significant correlation was found between the GET with duration on RRT ($r = -0.674$, $p = 0.016$) and a positive correlation with fasting blood glucose ($r = 0.673$, $p = 0.023$) in renal transplant patients.

There was a significant difference in the mean BUN level between each therapy subgroup ($p < 0.05$). The mean serum ferritin level was significantly higher, and the mean biceps skinfolds were significantly lower in hemodialysis patients than in peritoneal dialysis pa-

tients ($p < 0.05$). The mean serum creatinine level was significantly lower, and the mean albumin and HDL levels were significantly higher in patients with renal transplantation than in hemodialysis and peritoneal dialysis patients ($p < 0.05$). In addition, the mean Hb, total protein, t-chol levels were significantly higher, and the mean P and K⁺ levels were significantly lower in renal transplant patients than in hemodialysis patients ($p < 0.05$). The mean Ca⁺⁺ level was significantly higher in renal transplant patients than in peritoneal dialysis patients. Table 2 shows the patients' GET and biochemical and nutritional parameters.

Table 2. Parameters in the three-group analysis.

Replacement therapy	Hemodialysis	Peritoneal dialysis	Renal transplantation
GET (min)	85.1 $\pm$ 22.4	87.7 $\pm$ 31.8	94.6 $\pm$ 16.7
Hemoglobin (g/dL)	10.2 $\pm$ 2.1	11.6 $\pm$ 1.8	12.6 $\pm$ 2.3 [#]
BUN (mg/dL)	70.3 $\pm$ 22.3*	51.6 $\pm$ 20.9 [§]	25.6 $\pm$ 15.9 [#]
Creatinine (mg/dL)	9.1 $\pm$ 2.8	7.8 $\pm$ 2.7 [§]	1.5 $\pm$ 0.3 [#]
Glucose (mg/dL)	93.5 $\pm$ 11.8	96.1 $\pm$ 9.5	88.3 $\pm$ 8.9
Total protein (mg/dL)	6.5 $\pm$ 0.7	6.6 $\pm$ 0.7	7.2 $\pm$ 0.4 [#]
Albumin (g/dL)	4.0 $\pm$ 0.5	3.9 $\pm$ 0.3 [§]	4.5 $\pm$ 0.3 [#]
Total cholesterol (mg/dL)	157.1 $\pm$ 32.6	170.8 $\pm$ 38.7	185.5 $\pm$ 33.6 [#]
HDL-cholesterol (mg/dL)	40.1 $\pm$ 22.2	38.6 $\pm$ 8.8 [§]	59.8 $\pm$ 12.5 [#]
LDL-cholesterol (mg/dL)	89.0 $\pm$ 24.2	90.8 $\pm$ 30.5	103.3 $\pm$ 32.2
VLDL-cholesterol (mg/dL)	29.6 $\pm$ 15.3	39.8 $\pm$ 24.6	26.4 $\pm$ 5.8
Triglyceride (mg/dL)	150.1 $\pm$ 73.8	197.0 $\pm$ 118.4	141.0 $\pm$ 32.4
Calcium (mg/dL)	9.3 $\pm$ 1.0	9.1 $\pm$ 0.5 [§]	9.7 $\pm$ 0.3
Phosphorus (mg/dL)	5.5 $\pm$ 2.0	4.3 $\pm$ 1.2	3.4 $\pm$ 0.5 [#]
Na (mEq/L)	139.0 $\pm$ 6.3	139.4 $\pm$ 4.7	137.7 $\pm$ 5.6
K (mEq/L)	4.9 $\pm$ 0.8	4.3 $\pm$ 0.8	4.1 $\pm$ 0.4 [#]
PTH (0.8–5.2 ng/mL)	10.4 $\pm$ 11.8	13.0 $\pm$ 12.2	6.7 $\pm$ 4.8
Ferritin (μ g/mL)	533.4 $\pm$ 603.7*	215.3 $\pm$ 226.7	435.0 $\pm$ 704.2
Folic acid (3–16 ng/mL)	16.7 $\pm$ 8.1	11.3 $\pm$ 8.4	9.7 $\pm$ 79.9
Vit. B ₁₂ (160–800 pg/mL)	589.1 $\pm$ 386.5	627.0 $\pm$ 354.6	382.5 $\pm$ 225.4
Biceps skinfold (mm)	5.7 $\pm$ 1.8*	10.2 $\pm$ 5.0	6.8 $\pm$ 2.6
Triceps skinfold (mm)	9.2 $\pm$ 2.6	13.2 $\pm$ 5.0	12.0 $\pm$ 5.0

[#] $p < 0.05$, hemodialysis vs. transplantation.

* $p < 0.05$, hemodialysis vs. peritoneal dialysis.

[§] $p < 0.05$, peritoneal dialysis vs. transplantation.

DISCUSSION

In this study, GET was studied in hemodialysis, peritoneal dialysis, and renal transplant patients, all of whom were followed in the same center. GET was evaluated with the same method in the same nuclear medicine department and the results were compared with the GET of healthy subjects to avoid differences in the evaluation protocol of GET. The main findings of the present study are 1) the GET is more prolonged in patients on RRT than in healthy subjects; 2) the GET was not significantly different in patients dialyzed with hemodialysis and peritoneal dialysis when the peritoneal cavity was filled with the peritoneal dialysis fluid; and 3) renal transplantation did not offer a more beneficial effect on GET when compared with hemodialysis and peritoneal dialysis.

The characteristic symptoms of delayed GET are nausea, vomiting, early satiety, bloating, and weight loss. Diabetes mellitus, scleroderma, and neurologic disease including multiple sclerosis, and cerebrovascular events are well-known causes of gastroparesis. Neuropathy secondary to diabetes and amyloidosis, and drugs such as anticholinergics and dopaminergics, are also related to gastroparesis. According to our knowledge, the GET in patients with ESRD has been examined in previous studies, but GET was not investigated in hemodialysis, peritoneal dialysis, and renal transplant patients, and the results of each therapy subgroups were not compared with each other.

The mean GET time is longer in patients with ESRD who do not undergo dialysis treatment.^[4,12] Hemodialysis, peritoneal dialysis, and renal transplantation are the modern treatment modalities offered to patients with ESRD. One of the main purposes of these three RRTs is to revert the negative effects of ESRD in patients. Hemodialysis is one of the widely accepted therapies for patients with ESRD. The hemodialysis therapy is known to remove uremic toxins, and to prevent or at least delay uremic complications. However, the present study showed that the GET was not normalized by the standard effective hemodialysis therapy. This result complied with some of the previous studies.^[2,4,5] The previous studies showed conflicting results about the relationship between GET and dyspeptic symptoms.^[3-5,13] Soffer et al.^[13] found that GET was not different in normal subjects and hemodialysis patients with or without gastroparesis symptoms including nausea and vomiting or postprandial bloating. Whereas Van Vlem et al.^[5] found delayed GET in hemodialysis patients who had dyspeptic symptoms. In addition, a relationship has been shown between GET and biochemical parameters and nerve

function such as BUN, serum folic acid, intracorporeal folic acid, vitamin B₁₂, prealbumin, and the mean fibular nerve conduction velocity.^[2]

It has been reported that the GET of peritoneal dialysis patients was similar to the GET of healthy subjects when the patients' abdomens were empty.^[8,14] However, a significant delay in GET was reported when the patients' abdomens were full.^[6,8,11,14] In the present study, peritoneal dialysis patients were tested by using a technetium-99m labeled sulphur colloid scan method when their abdomens were filled with dialysate to obtain similar conditions as in normal daily life, because the majority of the peritoneal dialysis patients do daily activities such as eating, drinking, and sitting with dialysate fluid in the abdomen. Kim et al.^[6] investigated GET by using a technetium-99m labeled sulphur colloid scan method in 11 stable peritoneal dialysis patients and compared the results to that of the 14 healthy subjects. The GET of peritoneal dialysis patients was similar to healthy subjects when the patients' abdomens were empty, but a significant delay was noted when the patients' abdomens were full with dialysate. Schoonjans et al.^[8] reported that the GET determined with the 13C-octanoic acid breath test in peritoneal dialysis patients was not significantly different from the GET of healthy volunteers when the patients' abdomens were empty. On the other hand, they noted a significant prolongation when the patients were full with peritoneal dialysate. By contrast, Van Vlem et al.^[7] reported a significant prolonged GET with the 13C-octanoic acid breath test in peritoneal dialysis patients even when their abdomens were empty. Moreover, a more prolonged GET was also reported in the same patient population with glucose-containing dialysate. On the other hand, Fernstrom et al.^[11] reported an impaired GET in peritoneal dialysis patients predominantly in male patients. However, the GET did not change according to gender in all three RRT patient groups in the present study.

Among the immunosuppressants used after renal transplantation, MMF is thought to have the most gastrointestinal side effects. On the other hand, tacrolimus, a macrolide, is expected to have a beneficial effect on GET, because erythromycin and other macrolide antibiotics, which are known as motilin agonists, have prokinetic properties. Maes et al.^[15] reported that tacrolimus had a more beneficial influence on GET than cyclosporine in the patient group receiving steroid, azathioprine, and cyclosporine or tacrolimus. In addition, the patients took their immunosuppressants with the test meal and breath test analysis was used to determine the GET. However, none of those patients had been receiving MMF. In the present study, most of

the patients were receiving cyclosporine, ten of whom received MMF, and four patients received tacrolimus. The different effect of the immunosuppressive drugs on GET could not be determined due to the number of patients taking tacrolimus or other immunosuppressive drugs in this study. Although renal transplantation is advised to revert the effects of ESRD, the present study showed that the GET in renal transplantation patients receiving mainly steroid, cyclosporine, and MMF was not significantly different from the GET of hemodialysis and peritoneal dialysis patients. However, the GET inversely correlated with time in therapy in renal transplant patients. This result might show the possibility of the beneficial effect of renal transplantation on GET in the long term. The significant differences of laboratory parameters in renal transplant patients with hemodialysis and peritoneal patients were thought to be secondary to functioning graft in renal transplanted patients.

In conclusion, this study was undertaken to evaluate the GET in hemodialysis, peritoneal dialysis, and renal transplant patients and to determine if there is any difference between those three RRT groups. Although the mean GET was longer in those three replacement therapy groups than in healthy subjects, there was no difference between the three therapy groups. Peritoneal dialysis patients have their meal usually when the peritoneum is full with peritoneal dialysis fluid, which is why the peritoneal dialysis patients underwent the scintigraphic study when their abdomens were full. Renal transplantation is known as a better therapy than the other two therapy groups for relieving the disturbing effects of end-stage renal disease. However, the mean GET was not shorter in renal transplant patients than in the other two therapy groups.

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